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**Original Article**

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# Clinical and Electrocardiographic Characteristics of Patients with Brugada Syndrome: Report of Five Cases of Documented Ventricular Fibrillation

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Seiji Takashio MD, Toshihiro Honda MD, Junjiro Koyama MD,  
Yukinari Odagawa MD, Koichi Nakao MD

Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center

**Background:** Brugada syndrome is a disease in which idiopathic ventricular fibrillation (VF) sometimes occurs and causes sudden death. However, the clinical characteristics are still not fully understood.

**Patients and Methods:** Five patients with Brugada syndrome, and with spontaneous VF documented by electrocardiograms (ECGs), were included in this study. We examined their clinical and electrocardiographic characteristics.

**Results:** The mean age at the first VF/syncope episode was  $54.4 \pm 11.4$  years. The mean follow-up duration of the study was  $114.8 \pm 35.9$  months. In 4 patients, typical coved-type ST-elevation with a circadian change in  $>1$  right precordial lead (V1 to V3) was observed, and in the remaining patient it developed only after a pilsicainide test. VF was initiated by ventricular premature contractions (VPCs), which were almost identical to the preceding VPCs. While the isolated VPCs rarely occurred before VF in the patients whose late potentials were positive, in the patient whose late potential was negative, there were frequent episodes of VPCs before VF.

**Conclusion:** In this study, we presented variable clinical and electrocardiographic characteristics of the patients. The differences might suggest that several mechanisms are involved in the onset of VF in Brugada syndrome.  
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**Key words:** Onset of ventricular fibrillation, Late potential, Ambulatory electrocardiogram, Bradycardia, Conduction disturbance

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## Introduction

Brugada syndrome is an arrhythmic disorder with risk of sudden cardiac death (SCD) due to ventricular fibrillation (VF). The syndrome is electrocardiographically characterized by distinct

ST-elevation in the right precordial leads of an electrocardiogram (ECG). Since the first report of the disease,<sup>1)</sup> many clinical and basic studies have been performed to ascertain the pathophysiology. However, many aspects remain unresolved.

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Address for correspondence: Toshihiro Honda, MD, Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, 5-3-1 Chikami, Kumamoto 861-4193, Japan. TEL +81-96-351-8000 FAX +81-96-326-3045

We have followed 5 patients with Brugada syndrome, who have been documented with spontaneous VF since 2001. In this study, we retrospectively evaluated the clinical and electrocardiographic findings of these patients, and showed a variation in the electrocardiographic features and the mode of onset of VF.

## Patients and Methods

### Patients

The study comprised 5 consecutive patients with Brugada-like ECGs and episodes of electrocardiographically documented spontaneous VF. The patients had been admitted to our hospital for evaluation and treatment of repeated episodes of syncope or VF. Brugada syndrome was subsequently and definitively diagnosed when a typical coved-type ST-segment elevation was observed in >1 right precordial lead (V1 to V3), in the presence or absence of a sodium channel blocking agent.

### Methods

In order to exclude structural heart disease, all 5 patients underwent several procedures, which included both non-invasive (12-lead ECG, 2-dimensional echocardiography, treadmill exercise test), and invasive (cardiac catheterization including coronary angiography and ventriculography) examinations. An electrophysiological study (EPS), to determine inducibility of ventricular tachyarrhythmias, was performed in all 5 patients using a standard method. In brief, the electrical stimulation protocols consisted of single, double, and triple extrastimuli during pacing rhythm with a cycle length of 600 and 400 msec, and burst pacing up to 250 bpm. The coupling of the extrastimulus was reduced in 10-msec decrements to 200 msec, until refractoriness, or until polymorphic ventricular tachycardia or VF lasting > 30 sec was induced. The site of stimulation was the right ventricular apex and the right ventricular outflow tract.

Late potential was analyzed using a signal-averaged ECG system (MAC5000, Marquette). The ECG was recorded during sinus rhythm using Frank X, Y, Z corrected orthogonal leads. Signals from 300 beats were amplified, digitized, averaged, and then filtered with a high-cutoff frequency of 250 Hz and a low-cutoff frequency of 40 Hz. The following three parameters were calculated using a computer algorithm: (1) filtered QRS (f-QRS) duration, (2) root-mean-square voltage of the terminal f-QRS complex (RMS40), and (3) duration of low-amplitude signals < 40  $\mu$ V in the terminal f-QRS complex

(LAS40). Late potential was considered positive when more than 2 of the 3 criteria (f-QRS > 120 msec, RMS40 < 20  $\mu$ V and LAS40 > 38 msec) were met.

Ambulatory ECGs were recorded (FM-100, FUKUDA DENSHI) during hospitalization due to VF episodes, or when the patient visited the outpatient clinic (a total of 28 times overall). On these ECGs, the number of VPCs were counted and their coupling intervals were measured. All the patients underwent a pilsicainide test. The intravenous administration of 1.0 mg/kg of pilsicainide elevated the ST-level by an additional 0.2 mV and showed typical coved-type ST-elevation on at least one lead of V1 through V3 in all the patients.

After all the examinations had been performed, implantable cardioverter defibrillators (ICDs) were implanted in all the patients. Clinical follow-up was carried out at 3- to 6-month intervals at our outpatient clinic. Shortly after each episode of VF, the stored intracardiac ECG and other data obtained from the ICD, were analyzed.

## Results

### Clinical and electrocardiographic characteristics

The clinical findings of 5 Brugada patients with documented VF are summarized in **Table**. The mean age at the episode of VF/syncope was  $54.4 \pm 11.4$  years; all patients were male. No structural heart diseases were found in any patient. **Figure 1** shows the waveforms of the ECGs in the right precordial leads of each patient; there are some inter-patient differences. In 1 of the 5 patients (Case 1), the QRS morphology showed a complete right bundle block pattern, and typical coved-type ST-elevation appeared only after the administration of pilsicainide. In the other 4 patients (Cases 2 to 5), typical coved-type ST-elevation was observed in at least one lead. Circadian changes in the waveform of the ECG were observed in all the patients (not shown). The mean number of VF episodes, recorded on the ECG or in the stored intracardiac ECG from the ICD, was  $5.2 \pm 4.2$  (range, 1 to 11); these episodes were recorded over a mean follow-up duration of  $114.8 \pm 35.9$  months. All episodes of VF occurred during the night. An electrical storm, defined as > 3 episodes/day of VF and shocks of ICD, was observed only in Case 1. A family history of unexpected SCD was recognized in two cases. Late potential was positive in 4 of the 5 patients. The means for the three ECG parameters of interest were: F-QRS,  $140 \pm 13.2$  msec; RMS40,  $13.6 \pm 7.8$   $\mu$ V; and LAS40,  $47.0 \pm 18.5$  msec. VF was induced by EPS in only one patient.

**Table** Demographic and clinical characteristics of study patients

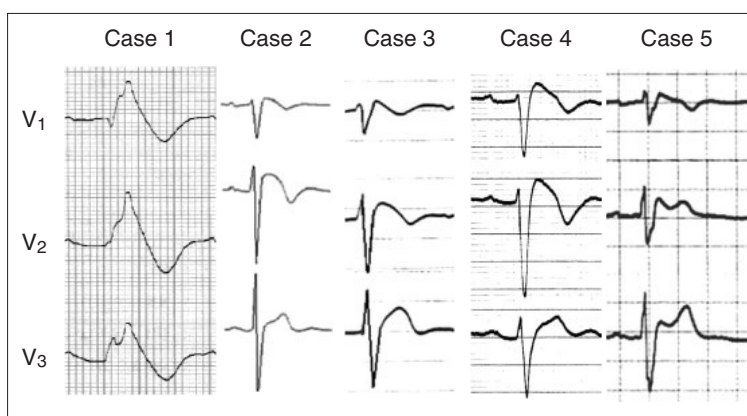
Case no.	Age at onset (years)	Gender	Follow-up duration (months)	First symptom	Family history of SCD	EPS	Number of VF episodes	Electrical storm	Late potential	Atrial fibrillation
1	65	Male	106	VF	Father: in his 60's Brother: at 40 y.o.	VF(+)	11	+	Positive	–
2	62	Male	92	VF	none	VF(–)	2	–	Positive	+
3	41	Male	110	VF	none	VF(–)	8	–	Negative	–
4	43	Male	177	VF	none	VF(–)	1	–	Positive	+
5	61	Male	89	Syncope	Brother: at 65 y.o.	VF(–)	4	–	Positive	+
54.4 ± 11.4*			114.8 ± 35.9*			5.2 ± 4.2*				

SCD: sudden cardiac death, EPS: electrophysiological study, VF: ventricular fibrillation, y.o.: years old.

\*mean ± standard deviation

**Figure 1** The waveforms of right precordial leads of the electrocardiogram (ECG) of the study patients.

The distinct type I ST-elevation is shown in at least one lead in the ECG of each patient. The QRS configuration is indicative of a complete right bundle branch block in Case 1, and in this patient only, the ST-elevation appeared after administration of pilsicainide.



The mean number of VPCs, with a coupling interval of <0.60 sec, was  $10.1 \pm 23.1$  beats/day, as documented on the ambulatory ECGs of these patients. Even on the 2 days when VF occurred in Case 1, the numbers of VPCs were only 2 and 3 beats/day, respectively. The mean coupling intervals of all the VPCs was  $0.45 \pm 0.10$  sec.

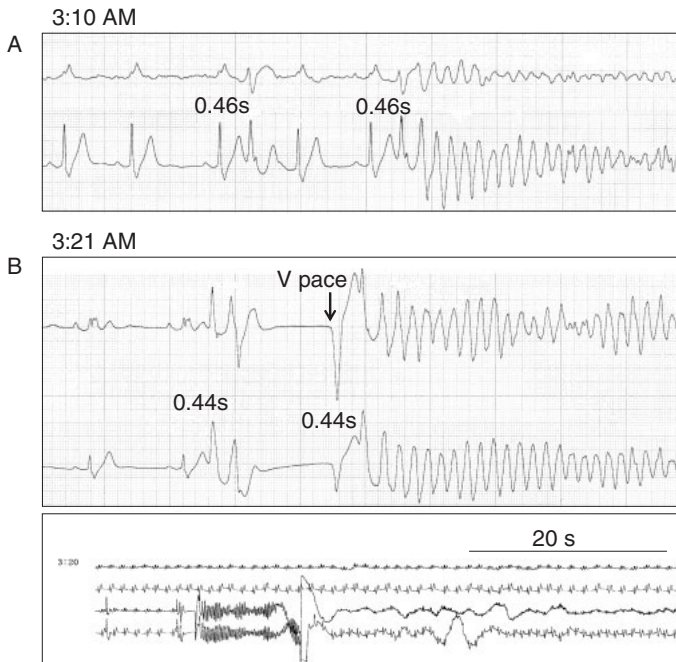
#### The mode of onset of spontaneous VF

The onset of VF was recorded in 3 of the 5 patients within the group. In Case 1, the occurrence of VF was identical to that of the VPC with a coupling interval of 0.46 sec (Figure 2A). In the same patient, another pattern of VF onset was observed (Figure 2B). After a post-VPC pause generated by a VPC couplet, the next coupling interval of 0.44 sec initiated an episode of VF. That is, VF occurred after the long-short RR intervals. In Case 2, the episode of VF was also initiated by only one VPC, with coupling interval of about 0.40 sec (Figure 3A). In these two patients, VPCs were observed rarely (Figure 2B and 3A). On the other hand, in Case 3, VPC couplets, with coupling interval of 0.35 sec and the next R-R interval of 0.30 sec, occurred frequently

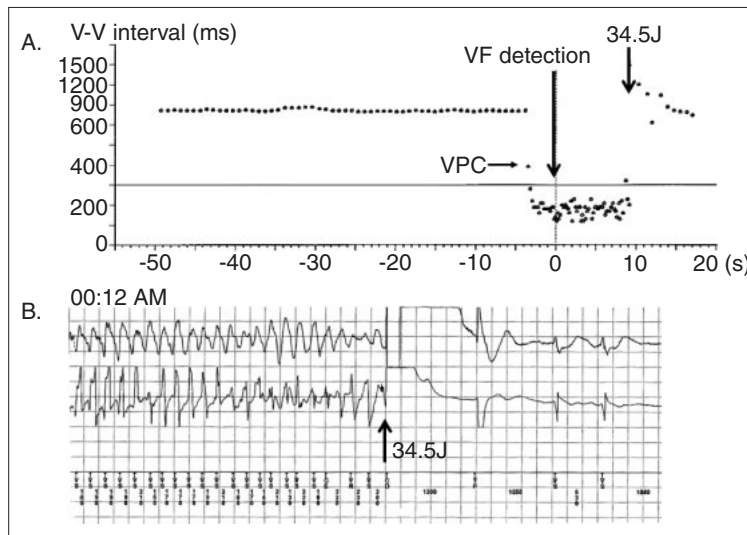
and identical couplets initiated VF (Figure 4A). The same finding was seen on the stored ECG obtained from the ICD of this patient (Figure 4B). In Case 4, junctional bradycardia continued after the VF episodes (Figure 5). An AAI pacemaker was implanted because of the continuation of the bradycardia, and was later upgraded to a DDD-type ICD against Brugada syndrome. No further episodes of VF have been documented in this patient during a follow-up period of 177 months, after 60 ppm of atrial pacing by the AAI pacemaker or the ICD.

#### Discussion

In this study, we have presented the typical ECG waveform in 5 patients with Brugada syndrome and spontaneous VF. The onset of VF was documented in 3 of the 5 patients. The other characteristics of the study patients were: they were all middle-aged males, the VF occurred during the night, circadian changes in the waveform of the ECGs were observed, and typical coved-type ST-elevation (type I ST elevation)<sup>2)</sup> was observed before or after administration of pilsicainide. In 4 of the 5 patients,



**Figure 2** The onset of ventricular fibrillation (VF) initiated by ventricular premature complexes (VPCs) from Case 1 recorded on an ambulatory ECG (A) Preceding VPC with coupling interval of 0.46 sec, and VF initiated by the second VPC, are shown. (B) VF was initiated by a VPC with coupling interval of 0.44 sec after a compensatory pause caused by a preceding VPC couplet. The small ECG strip at the bottom of the figure presents the onset of VF and the restoration of sinus rhythm by a defibrillator shock. VPCs were observed only rarely before the VF and the electrical shock.



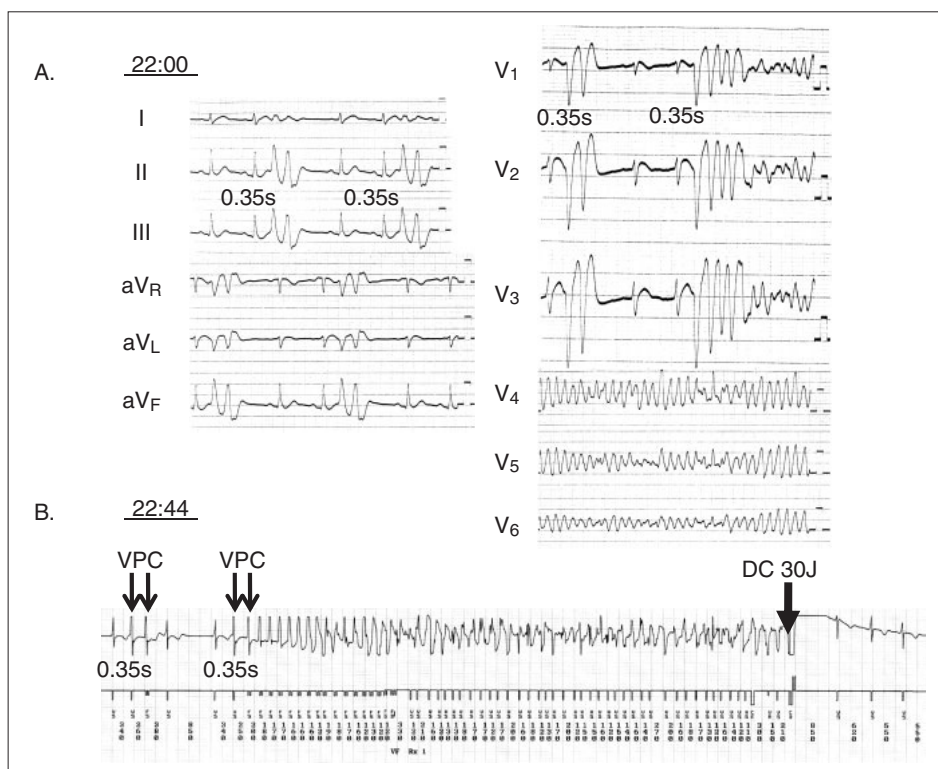
**Figure 3** (A) The onset of VF induced by a VPC with coupling interval of 0.40 sec. (B) A defibrillating shock by an implantable cardioverter-defibrillator (ICD), as seen on the stored data and intracardiac ECG obtained from the ICD of Case 2.

VF also recurred after ICD implantation, and shocks of the ICD during a mean follow-up duration of  $114.8 \pm 35.9$  months. These findings indicated that these patients were clearly at high risk of SCD, as seen in previous studies.<sup>3-5)</sup>

We observed the occurrence of VPCs and the onset of VF on the ambulatory ECGs, the stored ECGs, and the 12-lead ECGs in these patients. However, VPCs were rarely observed on ambulatory ECGs ( $10.1 \pm 23.1$  beats/day), and their coupling intervals were relatively long ( $0.45 \pm 0.10$  sec). In fact, in Case 1 on the days when VF occurred, the

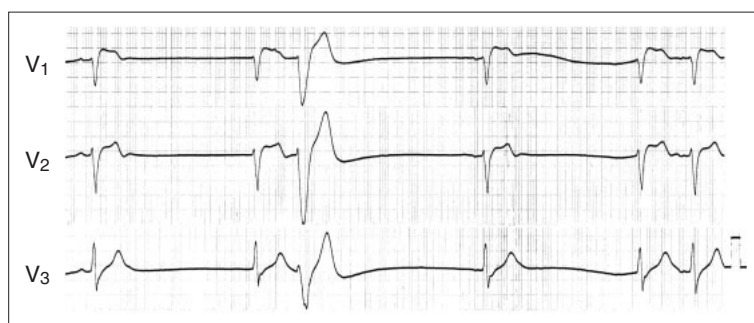
number of VPCs was very rare on the ambulatory ECG. The findings suggest that ambulatory ECGs are not useful for identifying patients at high risk of SCD or for predicting the occurrence of VF.

It has been reported that episodes of VF were preceded by VPCs which were almost identical to the initiating VPCs of VF, and that VF attacks were always initiated by the same respective VPCs.<sup>6)</sup> Similar results were seen in two patients in our study (Cases 1 and 2) in whom VPCs were recorded. In Case 1 and Case 2, VPCs were observed rarely or not at all, even just before the onset of VF on the stored



**Figure 4** The onset of VF in Case 3, as recorded on a 12-lead ECG and on the stored ECG from the ICD. The ECG was recorded with a 3-channel ECG recorder.

(A) The onset of VF initiated by a VPC couplet was documented on the 12-lead ECG. Before the onset, VPC couplets with an identical morphology to left bundle branch block and inferior axis were frequently observed. (B) The onset of VF and the restoration of sinus rhythm by a defibrillating shock are shown on the stored ECG from the ICD. A preceding VPC couplet occurred with the same coupling interval as in **Figure 4(A)** and the second VPC couplet initiated the episode of VF. The pattern of onset of VF was similar to that in **Figure 4(A)**.



**Figure 5** Junctional bradycardia (HR; 33 bpm) with ST elevation in leads V1 through V3 continued after termination of VF episode (Case 4). An episode of VPC and sinus beats was also observed.

ECG from the ICD. Then, a single VPC induced VF, as shown in **Figure 2** and **Figure 3A**. On the other hand, in Case 3, VPC couplets frequently occurred before the onset of VF, and eventually initiated VF, as shown in **Figure 4**. The clear difference in the onset mode of VF suggests that two types of mechanisms are involved.

It is widely accepted that the mechanisms of ECG waveform of Brugada syndrome, and the onset of VF in the syndrome, are mainly due to abnormal

repolarization.<sup>7,8)</sup> In brief, the loss of the action potential dome in the right ventricular epicardium, due to a larger transient outward potassium current (Ito) than in endocardium, creates a voltage gradient and results in ST-elevation in the precordial leads. When the transmural voltage gradient is increased heterogeneously, VF occurs due to phase 2 reentry. It has also been suggested that abnormal depolarization and/or conduction disturbance needs the maintenance of VF.<sup>9)</sup> In fact, type I ST-elevation was

observed before or after administration of pilsicainide in all 5 patients. On the other hand, in Case 3 of this study, in whom VF occurred in the second type of onset mode as shown in **Figure 4**, late potential was negative (**Table**). In this case, the conduction disturbance might be less important to the onset of VF.

It has been reported that a prolonged RR interval augmented the J wave and ST segment elevation of the next beat.<sup>10)</sup> The long-short RR sequence may enhance and influence repolarization prolongation.<sup>11)</sup> In Case 1 of this study, VF occurred after the long-short RR intervals (**Figure 2B**). In Case 4, after the first onset of VF, bradycardia continued (**Figure 5**), but atrial pacing has successfully suppressed VF for a long period of time. This phenomenon might show that a prolonged R-R interval caused abnormal repolarization and triggered the onset of VF.

**Limitation of this study:** This was a single center study involving a retrospective analysis of a small number of patients, therefore we cannot verify our results. In order to achieve more robust data, a multicenter study will need to be conducted in a larger number of patients.

**In conclusion,** we recorded two different modes of onset of spontaneous VF. A single VPC induced VF in the patients whose late potentials were positive, while VPC couplets frequently occurred before the onset of VF in the patient whose late potential was negative. These different clinical features might suggest several mechanisms of onset of VF. The number of VPCs was usually small, and could not predict the onset of VF.

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